REMARKS/ARGUMENTS

I. Amendments

Prior to the instant Amendment, claims 1, 19-34 and 36-39 were pending in the application. The Examiner rejected each of claims 1, 19-34, and 36-39 in the February 10, 2005 Office Action ("the Office Action"), alleging lack of enablement (claims 1, 30-34 and 36-39) or lack of novelty (claim 19) or obviousness (claims 20-29). Applicants appreciate the Examiner's thoughtful comments.

In this Amendment, Applicants have canceled claims 1, 25, 30-34, and 36-39, without prejudice. Applicants expressly reserve the right to pursue the canceled claims, or related claims of greater scope, in this application or a related application.

Claim 19 has also been amended to improve its readability by replacing the term "comprising" with the phrase "wherein said vector comprises." Claim 19 has also been amended to describe the claimed composition as an "adenovirus vector." Support for this amendment may be found throughout the specification and in the claims as originally filed (*e.g.*, originally filed claim 25; Table 1 on page 9). Claim 25, which recited an "adenoviral vector," has accordingly been canceled (as noted above). Claim 26 has been amended to depend directly from claim 19, instead of canceled claim 25. No new matter is added by any of these claim amendments.

New claims 40-42 have been added which describe cells that are transfected with the adenoviral vectors of the preceding claims. Support for these claims may be found in the specification at, *e.g.*, page 20, lines 7-31; Example 8 on page 30; and Figure 10.

II. Rejections Under 35 U.S.C. § 102

The Examiner rejected claim 19 under 35 U.S.C. § 102(a) as being anticipated by Rutherford *et al.* (July 1996, *J. of Interferon and Cytokine Res.*, 16(7): 507-510). Specifically, the Examiner writes on page 8 of the Office Action:

> Rutherford *et al.* disclose a recombinant vector for expressing an interferon-α polypeptide in a mammalian cell, wherein the nucleic

> acid segment encoding the interferon-α polypeptide lacks a secretion leader sequence. The reference further discloses mouse L cells expressing non-secreted human interferon-α.

Applicants' amended claim 19 renders the Examiner's rejection moot. Rutherford does not anticipate Applicants' amended claim 19 because Rutherford does not disclose an adenovirus vector. On page 509 (*e.g.*, Fig. 3), Rutherford describes the use of a plasmid (ptkIFS+) which appears to have been constructed by Coulombe *et al.* (*Gene*, 46:89-95 (1986); a copy of this reference is cited in the attached Information Disclosure Statement accompanying this Amendment). Coulombe shows that the plasmid ptkIFS+ is derived from a polyomavirus construct comprising an SV40 origin of replication. *See* Coulombe *et al.* at page 91.

Because Rutherford does not disclose a composition comprising all of the elements recited in claim 19, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(a).

III. Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 20-33 under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 6,069,133 (Chiou *et al.*), Rutherford *et al.*, (July 1996), and Zhang *et al.* (April 1996, PNAS 93:4513-4518). Specifically, the Examiner argues on page 9 of the Office Action,

> [since] Rutherford *et al.* disclose the antiviral activity of intracellular interferon and Zhang *et al.* disclose using an adenovirus to deliver the interferon gene to cells *in vivo*, one of skill in the art would have been motivated to prepare adenoviral vectors comprising an interferon-α gene lacking the secretion leader sequence so that the vectors could be used for *in vivo* delivery of the gene which would then drive expression of intracellular interferon-α in cells.

Under 35 U.S.C. § 103(a), claims are obvious when one of skill in the art would be motivated to combine elements from various prior art references with the reasonable expectation that the intended combination will be useful. Applicants respectfully submit that one of skill in the art would *not* be motivated to combine the disparate elements appearing in the

cited references because the references, taken as a whole, teach away from the combination of those elements. More specifically, the cited references would not have motivated one skilled in the art to combine a *non-secreted* human IFN gene with an episomal vector such as an *adenoviral* vector for the purposes of, *e.g.*, achieving an anti-proliferative effect in transfected cells.

As noted above, Rutherford describes various experiments intended to determine whether the intracellular expression of human type I IFN-α in mouse cells can activate the transcription factor ISGF3 through a "cell surface independent pathway." *See* Rutherford at page 507. Rutherford then describes a key tool in its research kit: a mouse cell line (L1-F) containing "*stably integrated* copies of the plasmid ptkIFS+." (emphasis added) *See id.* Rutherford cites the Couloumbe *et al.* reference as the source of this cell line. Coulombe in turn notes that their murine cell lines "contain low-copy number *insertions* of our recombinant *gene*." (emphasis added) *See* Coulombe Abstract. Obviously, the plasmid vectors created by Coulombe were designed to effect the chromosomal integration of Coulombe's highly derived IFN gene.

At best, one skilled in the art could read Coulombe as teaching how to select cell lines which contain their specified stably-integrated plasmid (or a portion thereof) and which express IFN-α. However, the integrating property of Coulombe's plasmid is not the only ways in which the plasmid differs from the adenoviral vectors claimed by Applicant (or the adenoviral vectors claimed by Zhang *et al.*). Coulombe expressly describes the "many ways" in which "significant" modifications were made to the IFN-α1 gene encoded by their plasmid, in addition to removal of the IFN leader sequence. *See* Coulombe at page 89-90. These modifications included (1) changing 71 nucleotides of the naturally occurring human IFN-α sequence, (2) "destroying the integrity of repeated and complementary oligodeoxynucleotides in the coding region," and (3) the introduction of an intron that does not normally appear in the gene. *See id.* All of the above-mentioned modifications appear in the plasmid vector (*i.e.*, the plasmid ptkIFS+) which is incorporated into the genomes of Coulombe's murine cell lines.

Nothing in Coulombe suggests that episomal *adenoviral* vectors encoding non-secreted human consensus sequence IFN genes would be useful for changing the properties of transformed cells. In fact, Coulombe concludes on page 93 that their *chromosomally-integrated*

highly modified vector has "*no significant effect* on the properties of the [transformed murine] cells, which showed normal growth, inducibility of endogenous IFN genes, and susceptibility to virus infection." (emphasis added).

As discussed above, the Rutherford reference appears to be a follow-up study using cell lines which contain the "stably integrated copies of the plasmid ptkIFS+" that were constructed by Coulombe *et al.*[1] Rutherford reports an approximately 2-fold increase in virus resistance in cells carrying low copy numbers of the integrated modified IFN-α gene but does not explain the discrepancy in results reported by Coulombe with the same cell lines. *See* Rutherford at page 508. Rutherford also reports using the calcium phosphate coprecipitation procedure described by Coulombe to co-transfect SV-T2 cells[2] with Coulombe's ptkIFS+ plasmid and a second plasmid (pAluFF) in order to demonstrate that "the enhanced levels of 2-5A synthase [observed in cells comprising chromosomally integrated copies of Coulombe's intron-containing codon-altered IFN gene] were due to transcriptional activation by intracellular IFN . . ." *See id.* Thus, Rutherford appears to have used the SV40-derived ptkIFS+ vector to create yet another line of cells in which the intron-containing IFN-α gene created by Coulombe is "stably integrated."

One of the historically recognized advantages of adenoviral vectors is that they are not prone to integrate into chromosomes of transfected cells, thereby causing unwanted mutations. To the extent that Rutherford merely repeats Coulombe's creation of mouse cell lines which comprise stably-integrated modified IFN-α1 genes, Rutherford also teaches away from the creation of Applicants' episomally-replicating *adenoviral* vector comprising a *non-secreted* human IFN-α lacking artificial introns, just as Coulombe teaches away from Applicants' claimed vectors.

The remaining two references cited by the Examiner do not address the contrary teachings of Rutherford (or Coulombe). Chiou *et al.* specifically teach the effectiveness of *extracellular* IFN-α, stating that "rather than protecting cells directly, IFNs activate surrounding

[1] Both Coulombe and Skup, the only authors on the Coulombe paper, also appear as authors on the Rutherford reference.
[2] SV-T2 cells are defined by Rutherford on page 509 as "SV40-transformed Balbc3T3 cells."

cells by binding to IFN-specific receptors on these cells." The term "adenovirus" does not appear in the Chiou *et al.* patent. *See* Chiou *et al.* at col. 1, lines 14-15. Although Zhang *et al.* disclose adenoviral vectors comprising the human consensus IFN gene, they do not disclose Applicants' adenoviral vectors which encode a *non-secreted* IFN gene, nor do Zhang *et al.* disclose Applicants' claimed mammalian cell compositions which comprise such vectors. Taken together, the most charitable characterization of Zhang *et al.* and Chiou *et al.* is that they teach one skilled in the art that the *extracellular* expression or delivery of IFN may be beneficial in some circumstances.

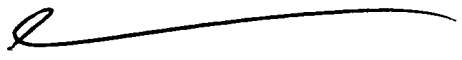
Applicants believe that the aforementioned shortcomings of each of the cited references is understandable. Applicants were the first to appreciate and demonstrate that adenovirus vectors encoding non-secreted human IFN-α could be used, for example, to target and decrease the rate of proliferation of mammalian cancer cells. Applicants therefore respectfully request withdrawal of the Examiner's rejections under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5004.

Respectfully submitted,



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Attachments